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AIR SAMPLING FOR CHEMOTHERAPEUTIC AGENTS: A LITERATURE REVIEW

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Little industrial hygiene data exist for the assessment of airborne levels of antineoplastic agents in the hospital work place. Persons handling these agents can be exposed by three potential routes: inhalation of aerosolized drug, transdermal absorption, and accidental ingestion resulting from lack of hand washing. Research has shown that by following all the procedures for handling cytotoxic drugs, the potential for exposure is minimal. All breathing zone air sampling results were below detectable limits. Various methods of air sampling had been used to measure concentration of antineoplastic drugs in drug preparation areas. None of these methods have been validated or standardized by the Occupational Safety and Health Administration (OSHA), American Conference of Governmental Industrial Hygienists (ACGIH), or the National Institute of Occupational Safety and Health (NIOSH).

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AIR SAMPLING FOR CHEMOTHERAPEUTIC AGENTS: A LITERATURE REVIEW

INTRODUCTION

Background

The base Bioenvironmental Engineer (BEE), Travis AFB, California, asked the Occupational Medicine Division, Armstrong Laboratory, for a sampling method for chemotherapeutic drugs (CD); also known as antineoplastic agents or cytotoxic drugs. The Oncology Clinic, DGMC, Travis AFB California uses approximately 18 antineoplastic drugs daily for the treatment of cancer in patients. Presently the Air Force, Occupational Safety and Health Administration (OSHA), American Conference of Governmental Industrial Hygienist (ACGIH), and the National Institute of Occupational Safety and Health (NIOSH) do not provide guidelines on air sampling procedures on antineoplastic agents.

Purpose

The purpose of this document is to review current information on air sampling for antineoplastic drugs. It also provides a summary of the main types of biological safety cabinets available.

Scope

This report provides base Bioenvironmental Engineers with current information on air sampling for antineoplastic agents and clarifies the difference between a regular lab hood and the biological safety cabinets used to control chemical exposure to cytotoxic drugs.

DISCUSSION

Definition of Terms

Drugs for the treatment of cancer are often referred to as chemotherapeutic agents, antineoplastic agents or cytotoxic drugs. Throughout this document the term antineoplastic agent will be used to refer specifically to anticancer drugs, except when quoting an article.

Characteristics of Antineoplastic Agents

Chemotherapeutic agents cause cell dysfunction or cell death in bacteria (antimicrobial), fungi (antifungal), parasites (antiparasitic), or host tissue (antineoplastic). They interact with deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein synthesis or cell division in living cells (1). Through these actions the potential for carcinogenic, mutagenic, and teratogenic effects is possible (2). Organ damage has been associated with chemotherapeutic drugs, both in animals and in human patients receiving long-term therapy.

There are three major categories of antineoplastic agents: alkylating agents, antimetabolites, and antibiotics. The alkylating agents are the most dangerous ones. They are extremely irritating to mucous membranes, eyes and

skin. Prolonged use of an alkylating agent has been associated with acute leukemia. Secondary tumors have also been observed in patients having undergone treatment with antineoplastic drugs (2).

Summary of Literature

The occupational hazards of a drug to an individual are determined by five variables (3):

a. The drug's chemical properties.
b. Susceptibility of the individual to the drug's toxic effects.
c. Cofactors, such as dietary habits, smoking, etc.
d. Number of exposures, magnitude of any one exposure, and cumulative amount of exposure.
e. Route of exposure, such as skin contact or inhalation.

Of these five interrelated variables, only (d) and (e) can be controlled to any substantial degree.

Routes of exposure to antineoplastic agents are primarily by inhalation of an aerosol, skin absorption and accidental ingestion from lack of hand washing. Exposure by inhalation can occur during drug preparation by opening an ampul, withdrawing a needle from vial or expelling air from a syringe. Skin contact can occur during administration of the drug, handling waste or contact with excrement.

The chronic effects of exposures to antineoplastic agents in very small concentrations remains a question. Several studies have attempted to assess indirectly the carcinogenic, teratogenic, and mutagenic risk posed by these drugs to hospital pharmacists and nurses (4,5). These studies examined the urine mutagenicity or evidence of chromosome damage in subjects who prepare or administer chemotherapy injections.

Several researchers have employed more direct methods of determining whether or not workers have been exposed to and absorbed antineoplastic drugs handled in the customary manner (6-9). Air sampling studies for the determination of fluorouracil, methotrexate, cyclophosphamide and doxorubicin have been conducted in the last ten years. Fluorouracil and cyclophosphamide, are the most widely studied of the antineoplastic agents (7,9). Cyclophosphamide is a known human carcinogen.

The first study, performed in 1981, attempted to develop a methodology to measure drug levels in the air that could be adapted to meet quality assurance programs in intravenous admixture areas (6). In this study, the authors used a Biotest RCS Centrifugal Air Sampler, generally used to measure microbial levels in air, adapted with a paper filter to measure airborne levels of fluorouracil. Measurements were made inside a horizontal laminar-flow hood. Drug manipulations were performed between the hood's filter and the Biotest. Drug collected on the filter was assayed with ultraviolet spectrophotometry after extraction. The range of fluorouracil collected by the Biotest was 0 - 14 µg or 0-0.07 µg/l of sampled air. This methodology could not guarantee that all air contaminated with drug was sampled. Also, the collection device was inside the laminar-flow hood and not at the operator's breathing zone. Therefore, no direct correlation can be made between the values obtained and the actual

exposure of the worker. Two studies, however, have been done for air sampling of fluorouracil at the breathing zone.

In one study, by Neal et al, air samples for fluorouracil, methotrexate, doxorubicin and cyclophosphamide were collected on an 47 mm, 0.5 µm pore size Teflon filter (7). Extraction with filtered distilled water acidified to pH 2.5 with phosphoric acid showed essentially a 100% recovery of fluorouracil, methotrexate, and doxorubicin and 75% recovery for cyclophosphamide. Detection limits were 1.5 ng or 1.6 ng/m^3 for methotrexate, 0.06 ng or 0.065 ng/m^3 for fluorouracil, 1 ng or 0.55 ng/m^3 for doxorubicin, and 30 ng or 120 ng/m^3 for cyclophosphamide. The coefficient of variation of the assays was 2-4%. Sampling rates were 1-4 l/min, and the sampling periods were 40 and 80 hours. Extracts were assayed by high-performance liquid chromatography (HPLC). Also, mass spectrometry (MS) was used to confirm the detection of fluorouracil, but the correlation between HPLC and MS was very poor. The second study for the determination of fluorouracil at breathing zone was made by McDiarmid et al in 1986 (8). This time a 37 mm Teflon filter was used instead of the 47 mm used in the previous study. In this study the flow rate was kept constant at 2 l/min. The detection limit for this study was 0.2 ng/m^3 using HPLC. Recovery was 95%.

In another study, air samples for cyclophosphamide collected on 37 mm glass fiber filters gave a better recovery from the filter: 97% (9). Samples were collected using personal sampling pumps at a flow rate of 2 l/min. Sampling times were 15 minutes to 2 hours. For the analysis, half of the samples were extracted with 1 ml sterile water and used for high performance liquid chromatography (HPLC) determination. Cyclophosphamide was monitored at 193 nm with a variable wavelength UV detector. The HPLC method used in this study allowed direct analysis of the water soluble cyclophosphamide. The detection limit of the method was 100 ng/injection or 1 µg/m^3. To confirm the HPLC method, the mass spectrometry (MS) method was developed. The advantages of the MS method are the high sensitivity and the stability of the samples after extraction into dichloromethane. The detection limit of the MS method was 2.5 ng/injection or 0.05 µg/m^3. The correlation between HPLC and MS method was good (r=0.987, slope 1.0737, n=13). See the table.

All samples taken outside the hood, when proper handling techniques for chemotherapeutic agents were followed, showed no detectable amount of any of these chemicals. On the other hand, detectable amounts were found when air samples were collected inside the hood, or proper handling techniques were not followed. Proper handling techniques include the use of an appropriate biological safety cabinet in conjunction with good aseptic technique and the recommended procedures for safe handling of antineoplastic agents. See AL-TR-91-0047, "Infectious and Hazardous Waste Protocol for Medical Facilities."

To provide the most current information on air sampling for antineoplastic agents, the following organizations were contacted: NIOSH, The National Institute of Cytotoxic Exposure, and Los Alamos Scientific Laboratory. None of these organizations are doing research on air sampling for antineoplastic agents at this time.

TABLE: SUMMARY OF LITERATURE

	FLUOROURACIL	METHOTREXATE	CYCLOPHOSPHAMIDE	DOXORUBICIN
SAMPLING INSTRUMENT	Biotest RCS Centrifugal Air Sampler Personal pump 47 mm, 0.5 µm Teflon filter and 37 mm, 0.5 µm Teflon filter	Personal pump 47 mm, 0.5 µm Teflon filter	Personal pump 47 mm, 0.5 µm Teflon filter and 37 mm, 0.5 µm Glass fiber filter	Personal pump 47 mm, 0.5 µm Teflon filter
DETECTION LIMIT (µg)	0 - 14	0.0015	0.0025 - 0.03	0.001
FLOW RATE (lpm)	1 - 4	1 - 4	1 - 4	1 - 4
COLLECTION TIME	5 min - 96 hrs	40 hrs, 96 hrs	15 min - 2 hrs, 40 hrs, 80 hrs	40 hrs, 80 hrs
RECOVERY FROM FILTER	95%-100%	100%	75% - 97%	100%
ANALYTICAL METHOD	HPLC, MS	HPLC	HPLC, MS	HPLC
SAMPLING AREA	Inside hood Breathing zone	Breathing zone	Inside hood Breathing zone	Breathing zone

Biological Safety Cabinets

Biological safety cabinets (BSC) are probably the most effective devices to control chemical exposure to antineoplastic drugs. A Class II cabinet offers the additional capability and advantage of protecting materials contained within it from extraneous airborne contaminants. This capability is provided by the high efficiency particulate (HEPA) filtered, recirculated mass airflow within the work space (10).

The National Sanitation Foundation (NSF) International describes, in its Standard 49, Class II Biohazard Cabinetry, Types A and B, biological safety cabinets with subtype designs. Type A cabinets maintain a minimum calculated average inflow velocity of 75 fpm through the work area access opening and have HEPA filtered downflow air from a common plenum. Type A units may exhaust HEPA filtered air back into the room, and may have positive pressure contaminated ducts and plenums (12,13). See Figures 1 and 2.

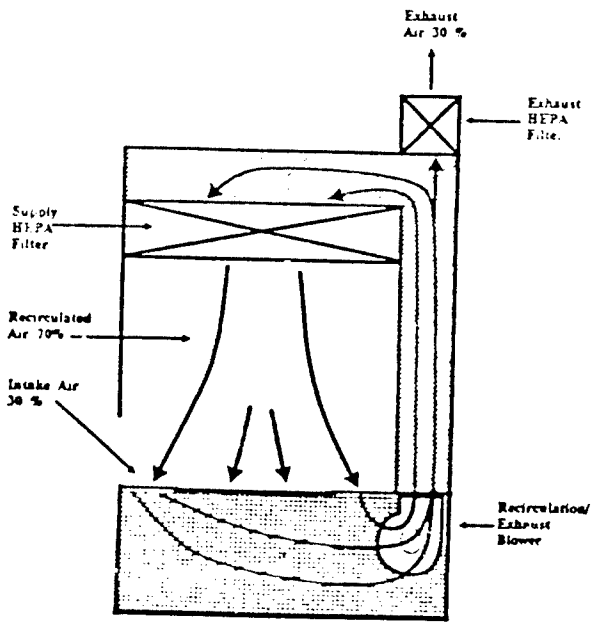


Figure 1. Class II, type A1 biological-safety cabinet. Adapted from Willcox GS, Mahoney CD, Welch JW et al. A comparison of Laminar airflow cabinetry. Cancer Chemother Update 1983;1(2):1-3.

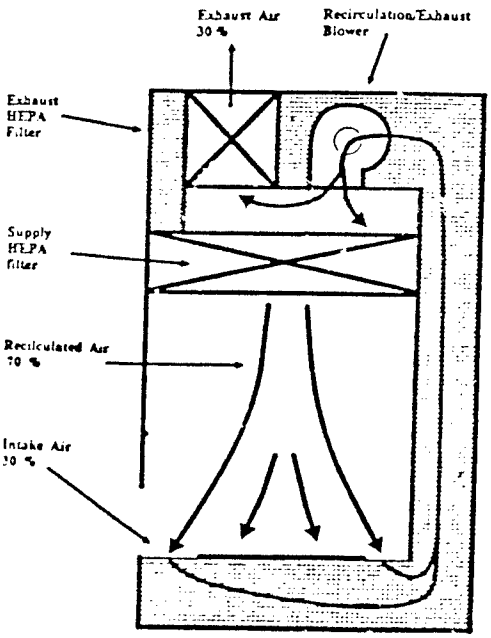


Figure 2. Class II, type A2 biological-safety cabinet. Adapted from Willcox GS, Mahoney CD, Welch JW et al. A comparison of Laminar airflow cabinetry. Cancer Chemother Update 1983;1(2):1-3.

For Class II Type B cabinets there are three designs, Figures 3 to 5. Type B cabinets maintain a minimum (calculated or measured) average inflow velocity of 100 fpm through the work area access opening (12,13).

a. Type B1 cabinets have HEPA filtered downflow air composed largely of uncontaminated recirculated inflow air and exhaust most of the contaminated downflow air through a dedicated duct exhaust to the atmosphere after passing through a HEPA filter.

b. Type B2 cabinets have HEPA filtered downflow air drawn from the laboratory or the outside air and exhaust all inflow and downflow air to the atmosphere after filtration through a HEPA filter without recirculation in the cabinet or return to the laboratory room air.

c. Type B3 cabinets have HEPA filtered downflow air that is a portion of the mixed downflow and inflow air from a common exhaust plenum and discharge all exhaust air to the outdoor atmosphere after HEPA filtration.

Type B units have all contaminated ducts and plenums under negative pressure, or surrounded by negative pressure ducts and plenums.

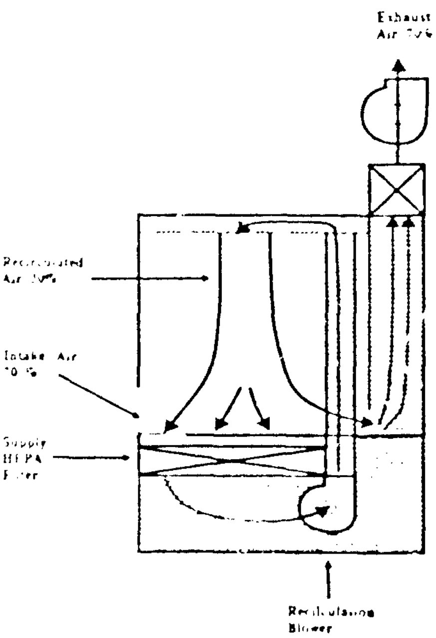


Figure 3. Class II, type B1 [illegible] safety cabinet. Adapted from [illegible] et al. A [illegible] of laminar [illegible] Cancer [illegible]

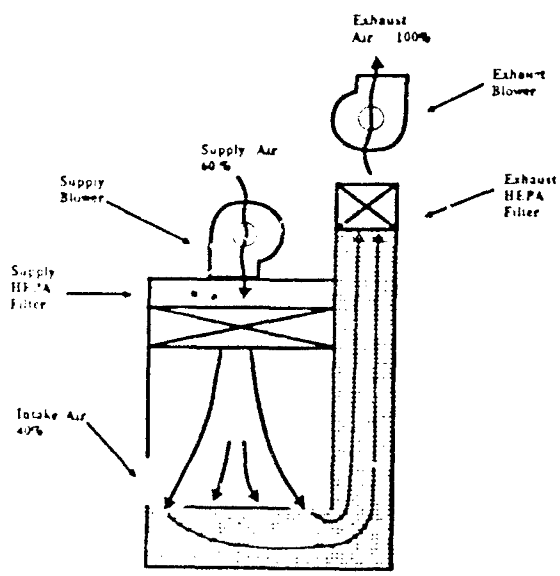
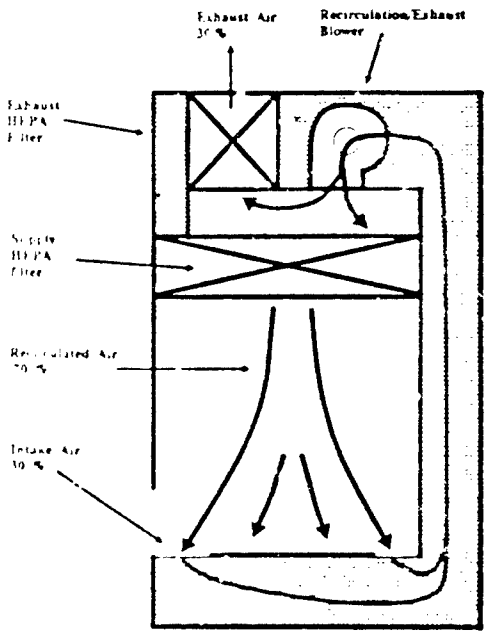


Figure 4. Class II, type B2 biological-safety cabinet. Adapted from [illegible] et al. A comparison of laminar airflow [illegible] Cancer Chemother Update [illegible]

It is imperative that Class II biological safety cabinets are tested and certified in situ at the time of installation within the laboratory or pharmacy, at any time the BSC is moved, and at least annually thereafter.

Courses on Biological Safety Cabinets Certification are offered by some organizations/universities every year. BSC are certified in accordance with the manufacturer's performance specifications and the National Sanitation Foundation (NSF) Standard Number 49, Class II (Laminar Flow) Biohazard Cabinetry (July 76, revised June 87). Personnel must be trained in the proper use of BSC. Of particular note are those activities which may disrupt the inward directional airflow through the work opening of the hood. Some demonstrated causes of the escape of airborne particles from within the cabinet are: repeated insertion and withdrawal of the workers' arms in and from the work chamber, opening and closing doors to the laboratory or isolation cubicle, improper placement or operation of materials or equipment within the work chamber, and brisk walking past the BSC while it is in use. Strict adherence to recommended practices for the use of BSC is very important in attaining the maximum containment capability of the equipment (10).



CONCLUSIONS

Little industrial hygiene data exist for the assessment of airborne levels of antineoplastics agents in the hospital work place. Persons handling these agents can be exposed by three potential routes: inhalation of aerosolized drug, transdermal absorption, and accidental ingestion resulting from lack of hand washing. Exposure by transdermal absorption and ingestion can be largely prevented by following the recommended safe handling procedures and wearing gloves, masks or goggles, and gowns (8).

Research has shown that by following all the procedures for handling antineoplastic agents the potential of exposure is minimal. All breathing zone air sampling results were below detectable limits. It is necessary for personnel dealing with antineoplastic agents to follow guidelines for handling, disposal and storage of these drugs. Biological safety cabinets have proven to be the most effective method of personal protection.

Various methods of air sampling had been used to measure concentration of antineoplastic drugs in drug preparation areas. None of these methods have been validated or standardized by OSHA, ACGIH or NIOSH; and very little data exits on the accuracy of the sampling methods. No correlation has been established between ambient air concentrations and health effects of antineoplastic agents.

RECOMMENDATIONS

Workplace Practices

Two elements are essential to insure proper workplace practices: education and training. Education includes understanding the hazards of antineoplastic drugs, their mutagenicity, and prevention of exposure. All persons dealing with antineoplastic agents should be trained in the correct procedures of handling, disposal and storage of antineoplastic drugs and the correct use of all the equipment. The "OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs" provides excellent guidelines to protect health-care workers from unnecessary exposure to antineoplastic agents (14).

Certification of Biological Safety Cabinets

The base BEE must ensure that each BSC has been certified annually. The following physical tests should be performed on site to qualify a Class II cabinet for certification (13):

1. Primary tests

    a. HEPA Filter Leak Test
    b. Velocity Profile
    c. Work Access Opening Airflow Test on BSC
    d. Airflow Smoke Patterns
    e. Cabinet Integrity Test: Soap bubble test

2. Secondary tests

    a. Vibration Test

b. Electrical Leakage
c. Noise Level Test
d. Lighting Intensity Test

A copy of the NSF International Standard 49 can be obtained by writing to the National Sanitation Foundation. Biological safety cabinet certification can be performed under contract if a trained person on these procedures is not available on base. NSF International is working on a proposed draft of revisions. Anticipated adoption of the revised Standard 49 is 11 Nov 91.

Air Sampling

Due to the lack of a validated method for air sampling, and no reliable correlation between ambient air concentrations and health effects, the Occupational and Environmental Health Directorate does not currently recommend any of these methods to measure concentrations of chemotherapeutic drugs in the workplace.

The local bioenviromental engineer or industrial hygienist needs to use professional judgment, based on the potential health effects and routes of exposure of these drugs, to determine what engineering controls and/or protective equipment provide the best protection to the person handling and administering antineoplastic drugs. Refer to AL-TR-91-0047, "Infectious and Hazardous Waste Protocol for Medical Facilities" for detailed handling procedures guidelines.

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GLOSSARY

Antineoplastic agents - inhibiting or preventing the development of neoplasm; an agent having such properties.

Biological safety cabinet (BSC), Class II. A laminar (streamline) flow, ventilated device, developed to protect: (1) personnel from harmful agents inside the cabinet, (2) the work, product, or procedure performed inside the cabinet from contaminants in the laboratory environment or from cross contamination inside the cabinet, and (3) the environment from contaminants contained in the cabinet.

Carcinogen - any cancer-producing substance.

Certification - to insure that biological safety cabinets meet standards of physical testing; usually filter integrity, cabinet integrity, air balancing, etc.

Chemotherapeutic agent - pertaining to chemotherapy; the use of chemical agents to treat disease; affect the causative organism unfavorably but do not harm the patient.

Cytotoxic agent - a chemical agent having a specific toxic action upon cells of special organs.

HEPA filter - high efficiency particulate air filter which have minimum efficiency of 99.97 percent in removal of particles 0.3 μm or larger. An HEPA filter removes only particles not vapors or gases.

High performance liquid chromatography (HPLC) - involves the use of very small particle size in column packing, with high pressures, to increase the rate of flow and shorten the separation time to few minutes. HPLC has become important for the separation of nonvolatile materials.

Mutagenic - any chemical agents that can induce genetic mutation.

Teratogenic - a chemical agent that can cause the production of physical defects in the developing embryo.

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